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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,750	04/17/2001	James P. Elia	1000-10-C01	7239
7590	02/16/2006		EXAMINER	KEMMERER, ELIZABETH
Gerald K. White GERALD K. WHITE & ASSOCIATES, P.C. 205 W. Randolph Street, Suite 835 Chicago, IL 60606			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/836,750	ELIA, JAMES P.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 09 January 2006.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 236,238-253 and 257-269 is/are pending in the application.
- 4a) Of the above claim(s) 240-242 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 236,238,239,243-253 and 257-269 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____.   |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>1/9/06</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input checked="" type="checkbox"/> Other: <u>Appendix A</u> .           |

**DETAILED ACTION*****Status of Application, Amendments, And/Or Claims***

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 21 November 2005 has been entered.

Claims 1-235, 237, and 254-256 are canceled. Claims 240-242 remain withdrawn from consideration as being directed to a non-elected invention, for reasons of record. Claims 236, 238, 239, 243-253, and 257-269 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Withdrawn Objections And/Or Rejections***

The rejection of claims 254 and 255 under 35 U.S.C. § 102(b) as being anticipated by Murry et al. as set forth at p. 22 of the previous Office Action (mailed 09 December 2004) is *withdrawn* in view of the canceled claims.

The requirement for a new title as set forth at pp. 26-27 of the previous Office Action (mailed 09 December 2004) is *withdrawn* in view of the newly submitted claims.

***35 U.S.C. § 112, First Paragraph – New Matter***

Claims 248, 249, and 252 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is of record.

Applicant's arguments (pp. 32-34, amendment received 21 November 2005) have been fully considered but are not found to be persuasive for the following reasons.

Applicant points to p. 45 of the specification as describing injecting growth factors into a patient intravenously, intraluminally, or intramuscularly to promote growth of an artery, and applying genes or other genetic material with an angioplasty balloon. This is not found to be persuasive because page 45, lines 13-16, of the specification reads as follows:

“VEGF proteins can be made in a lab and injected into a patient intravenously, intraluminally or intramuscularly to promote the growth of a new artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method.” (emphases added)

Clearly, this section of the specification is limited to use of proteins or nucleic acids (genes or genetic material). Regarding “intravenous” and “intraluminal” delivery, this section of the specification is limited to the suggestion of administering a protein. Nowhere else in the specification is it suggested that

cells should be administered intravenously or intraluminally. Regarding angioplasty delivery, the second sentence quoted above is limited to the suggestion of administering genes or other genetic material by angioplasty balloon. The specification defines "growth factors" as comprising cells, but does not define "genetic material" as comprising cells. For example, p. 31, lines 11-13, of the specification states "...the genetic material comprises comparable artificially produced genes, or genes harvested from other human beings or animals." Page 32, lines 8-9 state "genetic material can comprise comparable artificially produced genes or genes removed from another animal or otherwise generated." Page 35, line 4 clearly distinguished between growth factors (defined as encompassing cells) and genetic material: "genetic material plus growth factor(s) are implanted..." Page 35, lines 12-14 states "Genetic material is well conserved in nature. The Drosophila eyeless gene (ey), the mouse small ey gene (pax-6), and the Aniridia gene in humans are all homologous." Page 36, lines 25-26 state "Genes control structure and function. A gene or a bit of genetic material may act as a master control gene..." Clearly, the specification uses "genetic material" as pertaining to nucleic acids such as genes. It is also noted that one skilled in the art would only interpret "assistance of a vector," recited in the same sentence that uses "genetic material," as only applying to nucleic acids (genes or RNA or cDNA, etc.).

Applicant points to Capon v. Eshhar v. Dudas, 03-1480-1481 (CAFC 2005) as controlling precedent that 112 does not require recitation in the specification of features already known by workers in the technological field to

which the invention is directed. Applicant urges that the examiner mistakenly posited that generic inventions involving biochemical processes require a higher threshold for compliance with 112 because of a perception that success is not assured. Applicant argues that the Court in Capon observed that the USPTO must determine the sufficiency of support on a case-by-case basis given the state of the art at the time of the invention and in light of evidence of record. Applicant argues that the examiner has failed to address the generic concept that Applicant described – the concept of selecting a growth factor (herein the elected subgenus cells) and administering same into the body of a human patient using conventional methods and apparatus to achieve the goals of the claims.

Applicant addresses prior art, evidence of experimental verification (enablement) and potential viability of the concept. Applicant characterizes the examiner's rejection as being based on lack of working examples. This is not found to be persuasive because the instant fact pattern is distinct from that in the case law cited by Applicant. Capon v. Eshhar, 76 USPQ2d 1078 (CAFC 2005) concerns whether or not claims to chimeric DNA molecules are adequately described by a generic description. The issue was written description of products, not method steps. The issue here is not whether or not workers in this technology already knew the features of the cells recited in the claims; rather, the issue is that the instant specification did not set forth contemplation of a method step wherein cells were administered intravenously, intraluminally, or via angioplasty. As discussed in the previous paragraph, the instant specification did not set forth contemplation of such method steps. The claims are being examined to the

extent they read on the elected invention, administration of cells, and thus the generic concept of growth factor is not relevant. Remarks concerning prior art and enablement are not germane to the instant new matter rejection. Finally, the instant rejection is not based upon lack of working examples, but rather upon a detailed analysis of the specification. See preceding paragraph. Furthermore, MPEP § 2163.02 reads:

"An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."

In the instant case, none of these criteria have been met. There was no reduction to practice, and the specification only refers to method steps involving proteins, genes and "genetic material," *but not cells*, as being useful in intravenous, intraluminal and angioplasty delivery. Therefore, the rejection is maintained.

### **35 U.S.C. § 112, First Paragraph - Enablement**

Claims 236, 238, 239, 243-253, and 257-269 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it

is most nearly connected, to make and/or use the invention. The basis for this rejection is of record. See pp. 6-20 AND 22-26 of the previous Office Action (mailed 09 December 2004).

Applicant's arguments (pp. 34-35, amendment received 21 November 2005)

Applicant argues that the rejection must fail considering the totality of the evidence. Applicant urges that the specification describes standard systems of identification as well as known procedures for selecting and isolating known cells (bone marrow stem cells) and known apparatus and methods for administering such cells to achieve the desired therapeutic result. Applicant indicates that specification describes specific materials and administration routes. This has been fully considered but is not found to be persuasive. Applicant does not point to any specific section of the specification as supporting these statements. The previous Office Actions have reviewed the specification's teachings and found that they do not provide enablement for the instant claims.

Applicant argues that the examiner has failed to consider the generic concept of selecting well-known appropriate cells and administering such cells using well-known methods and apparatus to grow muscles and arteries in a human patient's heart that do not occur in nature. Applicant urges that the examiner has failed to cite any evidence in the record showing this concept in the prior art. This has been considered but is not found to be persuasive in that it is a confusing argument. Is Applicant admitting that the claimed methods were so well known in the prior art that the specification need not have disclosed anything

in addition to the prior art? Also, if the examiner had found evidence that the concept occurred in the prior art, then no enablement rejection would have been made. However, prior art rejections under 35 U.S.C. §§ 102 and 103 may have been made. Finally, the written description requires that the specification set forth what Applicant contemplates as the invention. It is improper to pick and choose among unconnected sections of a specification in an attempt to capture another research group's post-filing date discoveries.

Applicant argues that evidence has been submitted to support enablement of the claimed methods. Applicant points to the Perin et al. trials as evidence that nothing more than routine experimentation was required to carry out the technique. Applicant characterizes Perin et al. as following Applicant's basic regimen. This has been fully considered but is not found to be persuasive. The Perin et al. evidence has already been considered. Perin refers to "transendocardial" injections of cells and "intramyocardial" injections of cells, both of which appear to be intramuscular forms of administration. Thus, Perin also cannot be used to support enablement of the rejected claims which recite intravenous or intraluminal administration of cells.

### ***35 U.S.C. § 112, Second Paragraph***

Claim 245 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis of this rejection is of record.

Applicant's arguments (pp. 28-32, amendment received 21 November 2005) have been fully considered but are not found to be persuasive for the following reasons. Applicant correctly points out a typographical error in the previous rejection, wherein claim 254 was mistakenly rejected under this section. Claim 245 was intended to be rejected.

Applicant reviews the recent finding in Phillips v. AWH Corporation (75 USPQ2d 1321) that claims are generally given their ordinary and customary meaning in the art, and that claims should be read in the context of the disclosure. Applicant argues that Phillips states that extrinsic evidence is less significant than the intrinsic record. Applicant points to the finding in Phillips that dictionary evidence can be useful, but such evidence is less reliable than specifications and prosecution histories. Applicant argues that the examiner should interpret the words "multifactorial and non-specific" in light of the specification, giving the words their ordinary meaning. Applicant argues that the examiner's interpretation is based on non-contextual sources places the terms out of context and do not enjoy the same weight of evidence as the specification. This has been fully considered but is not found to be persuasive. The examiner takes no issue with the general principles discussed in Phillips. The specification was the first place consulted by the examiner to breathe life and meaning into the term "multifactorial and non-specific" as applied to cells. As explained previously on the record, neither the specification nor the art provides an unambiguous definition for the term. Page 37 of the specification states, "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the

necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." The use of "such as" clearly implies that the term "multifactorial and non-specific cells" is intended to encompass cells other than stem cells and germinal cells. However, neither the specification nor the art disclose what these other cells are. In the absence of this information, the skilled artisan cannot determine the metes and bounds of the claims at issue. The functional portion of the definition, "...provide[s] the necessary in vivo and in vitro cascade of genetic material ..." makes no sense. What is a cascade of genetic material? Thus, the specification does not define these terms, and the metes and bounds of the claimed invention cannot be determined. A search of the prior art indicated that the relevant art also does not use the terms "multifactorial and non-specific" in connection with cells. See Appendix A, submitted as evidence, regarding a search done in the database Medline. The first result uses "multifactorial" to describe diseases. The second result uses "multifactorial" to describe a process. The third result uses "multifactorial" to describe a process. The fourth result uses "multifactorial" to describe analyses. The fifth result uses "multifactorial" to describe a process. The sixth result uses "multifactorial" to describe a study. Each of these usages is consistent with the examiner's position that the term "multifactorial," given its ordinary and customary usage in the art, is used to describe causes, effects and processes, not cells.

Applicant argues that the examiner's position is supported by a lack of search results regarding the terms followed by a series of suppositions and

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speculations regarding the meaning of the terms. Applicant characterizes the examiner's position as amounting to nothing more than opinion due to lack of evidence. Applicant indicates that while a chemist may interpret "multifactorial" to be limited to describing a process, one in the medical arts would not. Applicant urges that the term "factor" is well known in the medical art, and that "multifactorial" would be understood by one in the medical art to mean more than one factor. This has been fully considered but is not found to be persuasive. The rejection is supported by evidence. See discussion of the specification and attached search results. Applicant has provided no evidence that chemists and medical artisans would interpret "multifactorial" in different ways. Finally, Applicant's definition of 'multifactorial' as meaning "more than one factor" makes no sense when applied to cells. What is a "more than one factor cell?"

Applicant refers to the fifth supplemental IDS as providing definitions. Applicant argues that the definitions are confirming evidence that the disputed terms are known and used properly in the specification, and that the IDS identifies the terms as adjectives. This has been fully considered but is not found to be persuasive. Regarding the dictionary definitions provided by the fifth supplemental IDS, the dictionary.net's definition of multifactorial is "involving or depending on several factors or causes (especially pertaining to a condition or disease resulting from the interaction of many genes)." This supports the rejection in that the term "multifactorial" is not used to describe cells. It is used to describe a cause (for example, of the disease) or an effect (for example, of the genes). Similarly, the dictionary.net's definition of nonspecific is "not caused by a

specific agent; used also of staining in making microscope slides; 'nonspecific enteritis' supports the rejection. "Nonspecific" is not used to describe cells. How can cells be "not caused by a specific agent?" The definition uses the term to describe causes (i.e., nonspecific enteritis is a disease caused by undefined factors). The selection of thesaurus words quoted by Appellant ("...undestined, undetermined, undifferentiated...") is also problematic. Cells can be in various stages of differentiation. For example, an embryonic stem cell would clearly be completely undifferentiated, as it can differentiate into any cell type. However, a promyelocyte is "undifferentiated" to an extent in that it can differentiate into a basophil, eosinophil, or neutrophil, whereas it cannot differentiate into any other cell type (e.g., keratinocytes, neural cells, muscle cells). The instant specification does not clarify whether such intermediate cells are encompassed by the term "multifactorial and non-specific."

Applicant provides definitions from Merriam Webster's Medline Plus Medical Dictionary, namely:

Factor: (noun) a substance that functions in or promotes the function of a particular physiological process or bodily system.  
Multifactorial: (adjective) having, involving, or produced by a variety of elements or causes.

Applicant argues that "factor" means a substance such as a cell that promotes a particular physiological process, such as growth of an artery. Applicant argues that "multifactorial" is used to denote the quality of a cell when a variety of elements (factors) promote the growth of an artery. This has been fully considered but is not found to be persuasive. Applicant's definitions support the

rejection. Applicant equates “factor” with “cell.” Thus, substituting “cells” for “factors” in Applicant’s second sentence, “multifactorial” is used to denote the quality of a cell when a variety of elements [cells] promote the growth of an artery. This simply makes no sense. Regarding the Merriam Webster’s Medline Plus Medical Dictionary definition of multifactorial, what types of cells have, involve, or are produced by a variety of elements or causes?

Applicant argues that the terms were understood by those skilled in the art, pointing to the second supplemental declarations of Drs. Heuser and Lorincz. The second supplemental declarations of Drs. Heuser and Lorincz submitted under 37 CFR 1.132 are insufficient to overcome the rejection of claim 245 based upon 35 U.S.C. § 112, second paragraph because, although the declarations use the term “multifactorial and non-specific cells,” they do not explain what cells are encompassed by the term. See section 7 of each of the Heuser and Lorincz second supplemental declarations. In view of the totality of the evidence of record, which includes the specification, prior art of record, and declarations submitted under 37 CFR 1.132, an unambiguous definition of the term “multifactorial and non-specific cells” has not been provided.

Applicant points to the two Strauer et al. publications (2003 and 2005, of record and attached to the response). Specifically, Applicant points to p. 1656 of Strauer 2003 as stating that cardiac lesions are multifactorial. This has been fully considered but is not found to be persuasive because it supports the instant rejection. Strauer 2003 uses the term “multifactorial” to describe a disease, not cells.

Applicant points to Strauer 2005 as stating that the regenerative potential of bone marrow derived stem cells may be explained by any of four mechanisms, and that "mechanisms" are further referred to as "factors." Applicant argues that the cells can be described as four-factor cells, i.e., multifactorial. Applicant concludes that the totality of the evidence indicates that the rejection should be withdrawn. Applicant also argues that "non-specific" is synonymous with "non-specialized." This has been fully considered but is not found to be persuasive. Strauer 2005 uses "four mechanisms" to describe "regenerative potential," not the cells *per se*. Even if Strauer 2005 could be tortuously construed as describing bone marrow stem cells as multifactorial, Strauer 2005 only discusses bone marrow stem cells. The specification already indicates that stem cells are exemplary of "multifactorial and non-specific" cells. The issue is what cells other than stem cells and germinal cells can be considered multifactorial and non-specific, given that the art does not apply these terms to cells.

In view of the preponderance of the totality of the evidence, the rejection is maintained.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose

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telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



ECK

ELIZABETH KEMMERER  
PRIMARY EXAMINER

## APPENDIX

Dialog level 05.10.03D

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\*File 155: Medline has resumed updating.

Set	Items	Description
? s	(multifactorial (2N) cell?) and stem	
12971	MULTIFACTORIAL	
2761033	CELL?	
66	MULTIFACTORIAL(2N)CELL?	
143636	STEM	
S1	6 (MULTIFACTORIAL (2N) CELL?) AND STEM	
? t	s1/7/1-6	

1/7/1

DIALOG(R)File 155:MEDLINE(R)

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18357667 PMID: 16020348

Current concepts in ocular surface reconstruction.

Dogru Murat; Tsubota Kazuo

Tokyo Dental College, Chiba, Japan.

Seminars in ophthalmology (United States) Apr-Jun 2005, 20 (2)

p75-93, ISSN 0882-0538 Journal Code: 8610759

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Diseases that affect the limbal %%stem%% %%cells%% are %%multifactorial%% and present with different stages of severity. The most important features to be considered in evaluating these patients include the degree of limbal %%stem%% cell loss, the extent of conjunctival disease, and the presence and etiology of ocular surface inflammation. Other important factors are tear film and eyelid abnormalities, keratinization of the ocular surface, laterality of the disease process, health and age of the patient. Careful consideration of all of these factors help tremendously in tailoring the most suitable method of treatment for each patient. The management of severe ocular surface disease has benefited from numerous advances in recent years. At one time, available techniques for visual rehabilitation consisted of superficial keratectomy, use of artificial tears, tarsorrhaphy as well as lamellar and penetrating keroplasty. A lamellar or penetrating keroplasty procedure resulted in a stable surface only for as long as the donor epithelium was present and once the epithelium sloughed off, the ocular surface failed due to conjunctivalization. The last few decades enjoyed the development and, especially, progress of new ocular surface reconstruction techniques such as amniotic membrane transplantation, limbal %%stem%% cell transplant procedures, transplantation of cultivated oral mucosal or limbal %%stem%% cell sheets. This review will briefly focus on the indications and methodology of each procedure and the currently available clinical data on the results of these procedures. (66 Refs.)

Record Date Created: 20050715

Record Date Completed: 20050818

1/7/2

DIALOG(R)File 155: MEDLINE(R)  
(c) format only 2006 Dialog. All rts. reserv.

15341984 PMID: 15145210

Robust conversion of marrow cells to skeletal muscle with formation of marrow-derived muscle %%cell%% colonies: a %%multifactorial%% process.

Abedi Mehrdad; Greer Deborah A; Colvin Gerald A; Demers Delia A; Dooner Mark S; Harpel Jasha A; Weier Heinz-Ulrich; Lambert Jean-Francois; Quesenberry P J

Roger Williams Medical Center, Department of Research, Providence, RI 02864, USA. mabedi@rwmc.org

Experimental hematology (Netherlands) May 2004, 32 (5) p426-34,

ISSN 0301-472X Journal Code: 0402313

Contract/Grant No.: 1P22-RR-18757-01; RR; NCRR; P01-DK-5022; DK; NIDDK; P01-HL-56920; HL; NHLBI; R01-DK-2742; DK; NIDDK; R01-DK-49650; DK; NIDDK

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

**OBJECTIVE:** Murine marrow cells are capable of repopulating skeletal muscle fibers. A point of concern has been the "robustness" of such conversions. We have investigated the impact of type of cell delivery, muscle injury, nature of delivered cell, and %%stem%% cell mobilizations on marrow-to-muscle conversion. **METHODS:** We transplanted green fluorescence protein (GFP)-transgenic marrow into irradiated C57BL/6 mice and then injured anterior tibialis muscle by cardiotoxin. One month after injury, sections were analyzed by standard and deconvolutional microscopy for expression of muscle and hematopoietic markers. **RESULTS:** Irradiation was essential to conversion, although whether by injury or induction of chimerism is not clear. Cardiotoxin- and, to a lesser extent, PBS-injected muscles showed significant number of GFP(+) muscle fibers, while uninjected muscles showed only rare GFP(+) cells. Marrow conversion to muscle was increased by two cycles of G-CSF mobilization and to a lesser extent by G-CSF and steel or GM-CSF. Transplantation of female GFP to male C57BL/6 and GFP to ROSA26 mice showed fusion of donor cells to recipient muscle. High numbers of donor-derived muscle colonies and up to 12% GFP(+) muscle cells were seen after mobilization or direct injection. These levels of donor muscle chimerism approach levels that could be clinically significant in developing strategies for the treatment of muscular dystrophies. **CONCLUSION:** In summary, the conversion of marrow to skeletal muscle cells is based on cell fusion and is critically dependent on injury. This conversion is also numerically significant and increases with mobilization.

Record Date Created: 20040517

Record Date Completed: 20040624

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DIALOG(R)File 155: MEDLINE(R)  
(c) format only 2006 Dialog. All rts. reserv.

13036731 PMID: 11000981

Mobilization of peripheral blood progenitor cells for autografting: chemotherapy and G-CSF or GM-CSF.

Siena S; Bregni M; Gianni A M

The Falck Division of Medical Oncology, Ospedale Niguarda, Cai Granda,  
Milan, Italy.

Bailliere's best practice & research. Clinical haematology (ENGLAND)  
Mar-Jun 1999, 12 (1-2) p27-39, ISSN 1521-6926 Journal Code: 100900679

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The mobilization of haematopoietic progenitor %%cells%% is a %%multifactorial%% process, still poorly understood at the molecular level. Mobilized haematopoietic progenitors, as defined by the expression of CD34 cell surface molecule, comprise heterogeneous subpopulations of cells committed to different haematopoietic lineages. Haematopoietic progenitors may be mobilized by chemotherapy alone, haematopoietic growth factors alone, or by chemotherapy plus haematopoietic growth factors. The choice of a mobilization regimen that allows an optimal yield of progenitors with a minimum number of leukaphereses should incorporate, in most patients, a disease-specific chemotherapeutic agent(s) plus a haematopoietic growth factor, to be continued until completion of harvest.

(76 Refs.)

Record Date Created: 20001019

Record Date Completed: 20001019

1/7/4

DIALOG(R)File 155: MEDLINE(R)

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12278080 PMID: 9588003

Advances in hematopoietic %%stem%% cell culture.

Audet J; Zandstra P W; Eaves C J; Piret J M

Biotechnology Laboratory, University of British Columbia, Vancouver, Canada.

Current opinion in biotechnology (ENGLAND) Apr 1998, 9 (2) p146-51,  
ISSN 0958-1669 Journal Code: 9100492

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Recent advances in our understanding of the earliest stages of hematopoietic cell differentiation, and how these may be manipulated under defined conditions *in vitro*, have set the stage for the development of robust bioprocess technology applicable to hematopoietic cells. Sensitive and specific assays now exist for measuring the frequency of hematopoietic %%stem%% cells with long-term *in vivo* repopulating activity from human as well as murine sources. The production of natural or engineered ligands through recombinant DNA and/or combinatorial chemistry strategies is providing new reagents for enhancing the productivity of hematopoietic %%cell%% cultures. %%Multifactorial%% and dose-response analyses have yielded new insight into the different types and concentrations of factors required to optimize the rate and the extent of amplification of specific subpopulations of primitive hematopoietic cells. In addition, the rate of cytokine depletion from the medium has also been found to be dependent on the types of cell present. The discovery of these cell-type-specific

parameters affecting cytokine concentrations and responses has introduced a new level of complexity into the design of optimized hematopoietic bioprocess systems. (49 Refs.)

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11563022 PMID: 8875201

Role of the basal cells in premalignant changes of the human prostate: a %%stem%% cell concept for the development of prostate cancer.

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Institute of Pathology, University of the Saarland, Homburg/Saar, Germany.

European urology (SWITZERLAND) 1996, 30 (2) p201-5, ISSN 0302-2838

Journal Code: 7512719

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

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**OBJECTIVES:** Prostatic intraepithelial neoplasias (PIN) result from abnormal differentiation and proliferation processes within the prostatic epithelial cell system. Recent data indicate that basal cells are essentially involved in normal and abnormal growth patterns of the human prostate. **RESULTS:** The basal cell layer represents the proliferative compartment and most probably houses the prostatic %%stem%% cell population. Basal cells are targets of several regulatory factors including estrogens, androgens, epidermal growth factor and other nonsteroidal growth factors. During the malignant transformation of the prostatic epithelium (PIN), the basal cell layer loses its proliferative function which is transferred to secretory luminal cell types. These proliferative abnormalities are attended by severe regulatory disorders of the programmed cell death within the prostatic epithelial cell system. The Bcl-2 oncoprotein which blocks the programmed cell death in the proliferative compartment (basal cell layer) in normal conditions, extends to the secretory luminal cell types in high-grade PIN lesions. This, in turn, may increase the genetic instability of the dysplastic epithelium. During the process of tumor invasion, the transformed cells lose their basal cell-specific phenotype and acquire features of exocrine cell types which represent the major phenotype in common prostate cancer. At the point of stromal invasion, the transformed cells produce neoplastic basement membrane material which allows them to penetrate the extracellular matrix.

**CONCLUSION:** These data provide theoretical bases for a %%stem%% cell concept in the development of prostate cancer and highlights the importance of basal %%cells%% in this %%multifactorial%% process.

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11537242 PMID: 8850230

[T-cell-rich B-cell lymphoma: multifactorial study of 4 cases]

Linfoma B rico en celulas T: estudio multifactorial de cuatro casos.

Moreno M M; Fernandez-Flores A; Paradela A; Rodriguez J M; Ageitos A; Gonzalo I; Marcos B; Robledo M; Rivas C

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Sangre (SPAIN) Dec 1995, 40 (6) p471-7, ISSN 0036-4355

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**PURPOSE:** With the correlational study of four cases in several areas (clinic, morphoimmunological, ultrastructural and genetic) we try to valorate the still controversial entity known as T-cell rich B-cell lymphoma (TRBL), and establish some useful clues in order to settle down the differential diagnosis between TRBL, Hodgkin's disease (HD), and T-cell non-Hodgkin's lymphomas (TNHL). **PATIENTS AND METHODS:** Cases proceeded from Oncology Department, and had been firstly misdiagnosed either as HD (3 cases) or as TNHL (1 case). Biopsies were processed and stained in routine way, H&E, Giemsa and Wilder. Immunohistological study, using monoclonal antibodies against B-cells, T-cells, histiocytes, activation and proliferation markers, was also performed with avidin biotin peroxidase (ABC) method. Ultrastructural study was performed in three of the cases; two patients were studied by PCR and Southern blot. **RESULTS:** All of the cases showed a diffuse histological pattern, with variable fibrosis, and proliferation of venules and capillaries. Small lymphoid cells, being positive for CD3, were dominant. Large blastic cells, positive for CD20, some of them with a Sternberg-like appearance, could be found, in a spotty pattern. Histiocytes were abundant and positive to CD68. Proliferation index (Ki-67) ranged between 13 and 24.5% being the stain mainly positive for B-cells and in a certain extent, also for T-cells. Ultrastructural features were closer to those of the NHL than to the ones found in HD. Molecular study failed to prove any rearrangement. **CONCLUSIONS:** TRBL is a rare entity between B-cell NHL group. Diagnosis and differential diagnosis (mostly with HD and T-cell NHL) have to be properly made, because of the very distinct prognosis and therapy.

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